Association Between Ambulatory Systolic Blood Pressure During the Day and Asymptomatic Intracranial Arterial Stenosis

Chao-Ting Chen, Yan Li, Jin Zhang, Yan Wang, Hua-Wei Ling, Ke-Min Chen, Ping-Jin Gao, Ding-Liang Zhu

Abstract—It is unclear at what time-window of the day blood pressure (BP) is most closely associated with cerebrovascular damage. In this cross-sectional study, we examined the strength of association between intracranial arterial stenosis (ICAS) and systolic BP (SBP) across different time-windows using 24-hour ambulatory BP monitoring in 757 consecutively recruited patients with hypertension. ICAS was diagnosed with computerized tomographic angiography in 127 (16.8%) patients, of whom 64 (50.4%) had stenosis ≥50% and 82 (64.6%) had ICAS in ≥2 vessels. Patients with ICAS (142 mm Hg), especially of multiple vessels (145 mm Hg), compared with patients without ICAS (126 mm Hg), had significantly (P<0.001) higher early morning (05:00–07:59 AM) SBP. The differences remained significant (P≤0.015) after adjustment for cardiovascular risk factors and SBPs at other time-windows of the day. Multivariate regression analysis showed that consecutive 3-hourly mean SBPs during the day were significantly associated with ICAS (odds ratio for each 10-mm Hg increase, 1.28–1.38; P≤0.001). However, only mean SBP obtained between 05:00 AM and 07:59 AM remained significant for ICAS (odds ratio, 1.30; P=0.019) when all consecutive 3-hourly mean SBPs were forced into a single multivariate model. In conclusion, the present study showed a significant association between early morning SBP and asymptomatic ICAS in patients with hypertension after accounting for conventional cardiovascular risk factors. Our findings highlight the importance of morning SBP as a cardiovascular risk factor and should be validated in prospective studies. (Hypertension. 2014;63:61-67.)

Key Words: blood pressure monitoring, ambulatory ■ intracranial vascular disorders

Stroke is an enormous health issue in China, being the leading cause of death, and there are ≈7.5 million survivors, three fifth of whom have had an ischemic stroke.1 Intracranial arterial stenosis (ICAS), a common cause of ischemic stroke,2 is more prevalent among Asians than whites3,4 and may be a promising surrogate target for prevention of stroke. Hypertension is a well-established risk factor for both ischemic and hemorrhagic forms of stroke, as well as for ICAS.4,9 However, there are limited data on the significance of asymptomatic ICAS in patients with hypertension.

Ambulatory blood pressure (BP) monitoring provides diurnal BP readings,10 and 24-hour mean BP, especially systolic BP (SBP), is well established as a strong and consistent predictor of stroke.10–12 However, it remains unclear at which time-window epoch during 24 hours ambulatory BP is most significant as a risk predictor. Early morning is suggested as the most vulnerable period for the occurrence of stroke, during which BP exhibits a marked surge in patients with hypertension.13,14 Conversely, nighttime BP has also been demonstrated to be a stronger predictor of stroke15 or equally predictive for fatal and nonfatal combined cardiovascular events compared with daytime BP.16 No previous study has ever addressed the association between ambulatory BP and asymptomatic ICAS. We aimed to compare the strength of association between asymptomatic ICAS and ambulatory BP at different time-window epochs during the day. Because SBP is the dominant component of BP for cardiovascular risk in middle-aged and elderly people,17 we restricted analyses to SBP.

Methods

Study Population

This study was undertaken within the framework of an ongoing prospective study on the prognosis of asymptomatic intracranial arterial disease in patients with hypertension. Patients were consecutively recruited either from the outpatient clinic or from the ward of the Department of Hypertension at Ruijin Hospital, a tertiary public general hospital in Shanghai, China, from January 2005 to December 2010. Patients with hypertension were invited to participate in the study if they had ≥2 cardiovascular risk factors defined according to the Chinese hypertension guidelines18 and were willing to undergo an examination of brain using computerized...
Ambulatory BP Measurement

Ambulatory BP monitoring was performed with validated SpaceLabs 90217 monitors (SpaceLabs Medical, Redmond, WA). We programmed monitors to obtain BP readings at an interval of 30 minutes throughout the day. A valid recording was defined as ≥10 BP readings during the daytime (08:00 AM–5:59 PM) and ≥25 readings during the nighttime (11:00 PM–5:59 AM) for a duration 220 hours. According to the lifestyle of local residents and the definitions of daytime and nighttime for short clock-time intervals in our previous publication,19 we categorized 24 hours of a day into 4 common time-windows: early morning (05:00–7:59 AM), daytime (08:00 AM–5:59 PM), evening (6:00 PM–10:59 PM), and nighttime (11:00 PM–04:59 AM). For each individual ambulatory BP recording, SBP readings within each time-window, the consecutive 3 hours (eg, 05:00–7:59 AM or 08:00–10:59 AM), and for the whole day were respectively averaged for analyses.

Brain CTA

Brain CTA was performed according to standard definitions5 with a GE FX/I helical CT scanner (General Electric, Fairfield, CT). CTA acquisitions were obtained after a single bolus intravenous injection of 70 mL Optiray Ioversol 320 into the antecubital vein at a rate of 3 mL/s. Scanning covered the whole brain with 5-mm slice thickness down to the level of aortic arch. Images were reformatted in axial, sagittal, and coronal planes with 1.25-mm slice thickness and then read at a workstation using the software of AW4.4 vessel analysis independently by 2 experienced radiologists who were blind to clinical data. Arterial stenosis was defined as a lesion characterized by a decreased arterial internal diameter, calculated as the ratio of the diameter of the diseased artery at its most severe site divided by the diameter of a nearby normal segment. The greatest stenosis at an intracranial artery was chosen as being representative for each subject. The number of arteries with stenosis for each patient was also counted. The 2 radiologists had good agreement in the identification of ICAS (κ=0.93; P<0.001), ICAS degree (κ=0.91; P<0.001), and the number of affected arteries (κ=0.93; P<0.001). All disagreements were reviewed and adjudicated by a senior radiologist (H.-W.L.) for consensus.

Other Measures

In the outpatient clinic and inpatient ward, conventional BP was measured with a mercury sphygmomanometer in patients who had rested for ≥25 minutes in the sitting position. Three consecutive BP measurements with a 1-minute interval were taken at the nondominant arm by a trained investigator. Hypertension was defined as a mean conventional systolic BP ≥140 mm Hg or diastolic BP ≥90 mm Hg on ≥3 occasions or if the subject was taking antihypertensive medication.18 We administered a standardized questionnaire to collect information on lifestyle and medical history. Smoking was classified as never, past, and current use of tobacco. Body height and weight were measured without shoes and wearing light indoor clothing for the calculation of body mass index (weight [kg]/height [m2]). Venous blood samples were collected after overnight fast and analyzed for glucose and serum lipids by automated enzymatic methods. Diabetes mellitus was defined by self-reported diagnosis or as a fasting blood glucose ≥7.0 mmol/L or a postprandial 2-hour blood glucose ≥11.1 mmol/L or use of antidiabetic drugs.19

Statistical Analysis

For database management and statistical analyses, we used the Statistical Package for the Social Sciences version 13.0 (SPSS Incorporation, Chicago, IL). Means and proportions between patients with or without ICAS were compared using the Student t test and Fisher exact test, respectively. Means among 3 groups were compared using ANOVA. To search for significant correlates of ICAS, stepwise logistic regression analysis was performed with the following variables: age, sex, body mass index, 24-hour mean SBP, current smoking and alcohol consumption, log-transformed duration of hypertension, serum total cholesterol, diabetes mellitus, and use of antihypertensive drugs. The P value for the variables to enter and stay in the model was set at 0.05. To account for the effect of clustering, the multivariate-adjusted analysis also included the setting of the BP recordings, that is, outpatient clinic versus inpatient ward. Logistic regression analysis was used to examine the association of ICAS and mean SBPs at different time-windows. Because SBPs at different time-windows were highly correlated, we first used separate regression models for each and then explored the independent associations by forcing all SBPs at different time-windows of the day into a single model. Overfitting of the model was tested by the heuristic shrinkage estimate, where a value <0.85 suggested overfitting.21 We used the likelihood ratio test to examine whether adding early morning SBP would significantly improve the goodness of fit of the model. In further analysis to illustrate the independent association of early morning SBP with the severity of ICAS, we performed ordinal logistic regression analyses. The outcome variable indicating the degree of stenosis was coded as 0 (no stenosis), 1 (stenosis ≤50%), or 2 (stenosis >50%), and the variable indicating the number of arteries with stenosis was coded as 0 (no stenosis), 1 (1 artery), or 2 (≥2 arteries). Statistical significance was defined as a 2-tailed P<0.05.

Results

Participant Characteristics

Among 4187 screened patients, 1189 (67.1%) of 1772 eligible patients agreed to participate in the study. Compared with the nonparticipants (n=583), participants had a slightly longer history of hypertension (median, 11 versus 10 years; P=0.037) and were less likely to report drinking alcohol (10.3% versus 13.9%; P=0.037), but otherwise their characteristics were similar (P≥0.06) with regard to age, sex, smoker status, history of diabetes mellitus, and level of total cholesterol. For the present analysis, we excluded 3 subjects with poor CTA images, 407 subjects without ambulatory BP data, and 22 subjects with invalid ambulatory BP recordings (ie, recordings with a duration <20 hours [n=1] or <10 daytime [n=2] or 5 nighttime [n=19] readings).

A total of 757 patients were included in the present analysis, 229 (30.3%) from the outpatient clinic and 528 (69.7%) from the inpatient ward, and 444 (58.7%) men, 526 (69.5%) treated with BP-lowering drugs, and 120 (15.9%) patients with diabetes mellitus. The average (±SD) age was 60 (±12) years. The median (interquartile range) duration of hypertension was 11 (6–21) years. In all participants, 127 (16.8%) had asymptomatic ICAS (64 with stenosis ≥50% and 82 with stenosis at ≥2 intracranial arteries).

Factors Associated With ICAS

Table 1 shows that patients with ICAS were older, had greater body mass index, longer history of hypertension, and higher levels of ambulatory BP and total serum cholesterol, and were more likely to have diabetes mellitus than those without ICAS. In stepwise logistic regression analysis that considered age, sex, body mass index, 24-hour mean SBP, total
Table 1. Clinical Characteristics According to the Presence or Absence of Intracranial Arterial Stenosis in 757 Chinese Patients With Hypertension

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No Stenosis</th>
<th>Stenosis</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total, n (%)</td>
<td>630</td>
<td>127</td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>373 (59.2)</td>
<td>71 (55.9)</td>
<td>0.49</td>
</tr>
<tr>
<td>Current smokers</td>
<td>154 (24.5)</td>
<td>25 (19.8)</td>
<td>0.26</td>
</tr>
<tr>
<td>Current drinkers</td>
<td>78 (12.4)</td>
<td>9 (7.1)</td>
<td>0.09</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>90 (14.3)</td>
<td>30 (23.6)</td>
<td>0.009</td>
</tr>
<tr>
<td>On antihypertensive treatment</td>
<td>434 (68.9)</td>
<td>92 (72.4)</td>
<td>0.43</td>
</tr>
<tr>
<td>Age, y</td>
<td>59.0±11.7</td>
<td>67.1±12.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>25.2±3.2</td>
<td>26.0±3.3</td>
<td>0.01</td>
</tr>
</tbody>
</table>

Table 2. Odds Ratios Associated With 10-mm Hg Increase in Ambulatory Systolic Blood Pressure for Intracranial Arterial Stenosis in 757 Chinese Patients With Hypertension

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early Morning SBP</td>
<td>Unadjusted 1.47 (1.33–1.63)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>Adjusted 1.38 (1.23–1.54)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>Fully adjusted 1.26 (1.03–1.54)</td>
<td>0.025</td>
</tr>
<tr>
<td>Daytime SBP</td>
<td>Unadjusted 1.35 (1.21–1.51)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>Adjusted 1.38 (1.21–1.57)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>Fully adjusted 1.08 (0.86–1.34)</td>
<td>0.52</td>
</tr>
<tr>
<td>Evening SBP</td>
<td>Unadjusted 1.31 (1.18–1.46)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>Adjusted 1.34 (1.20–1.51)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>Fully adjusted 1.08 (0.87–1.35)</td>
<td>0.48</td>
</tr>
<tr>
<td>Nighttime SBP</td>
<td>Unadjusted 1.38 (1.25–1.53)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>Adjusted 1.32 (1.18–1.47)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>Fully adjusted 0.99 (0.80–1.23)</td>
<td>0.96</td>
</tr>
</tbody>
</table>

In adjusted analysis, the setting of SBP recording (outpatient clinic vs inpatient ward), age, body mass index, log-transformed duration of hypertension, and serum total cholesterol were included as covariates. In fully adjusted analysis, SBPs in the early morning (5:00–7:59 am), daytime (8:00 am–5:59 pm), evening (6:00 pm–10:59 pm), and nighttime (11:00 pm–4:59 am) were additionally forced into a single model. CI indicates confidence interval; and SBP, systolic blood pressure.

ICAS and Ambulatory SBP at Different Time-Windows

Patients with ICAS, compared with those without, had significantly (P<0.001) higher early morning (142 versus 126 mm Hg), daytime (139 versus 130 mm Hg), evening (138 versus 128 mm Hg), and nighttime (110 versus 117 mm Hg) SBPs. However, only the difference in early morning SBP (131 versus 128 mm Hg; P=0.012) remained significant after adjustment for age, body mass index, serum total cholesterol, and log-transformed duration of hypertension, and SBPs at other time-windows of the day.

Similarly, in both unadjusted and multivariate-adjusted logistic regression analyses, SBPs in the morning, daytime, evening, and nighttime were all significantly (P<0.001) associated with the presence of ICAS (Table 2). Each 10-mm Hg increase in SBP at any of the 4 time-windows was associated with 31% to 47% higher odds for the presence of ICAS. However, when SBPs at the 4 time-windows were simultaneously put into a single multivariate model, only SBP in the early morning (OR, 1.26; 95% CI, 1.03–1.54; P=0.025) remained significant for the presence of ICAS (Table 2). The

The likelihood ratio test showed that adding early morning SBP into the fully adjusted model, which included the above-mentioned covariates and SBPs in the daytime, evening, and nighttime, significantly improved the goodness of fit of the model (P=0.023). As shown in Figure 1, the independent association between early morning SBP and the presence of ICAS was linear. Patients in the highest quartile of early morning systolic blood pressure were significantly (P<0.001) more likely to have ICAS than those in the lowest quartile.
SBP had significantly higher odds (1.91; 95% CI, 1.17–3.13; P = 0.01) than the whole population.

By using an ordinal logistic regression model, we explored the association between the severity of ICAS and ambulatory SBPs at different time-windows. In multivariate-adjusted analyses, SBPs at all 4 time-windows were significantly (P < 0.001) associated with the degree of ICAS and the number of arteries with stenosis (Table 3). Figure 2 shows that patients with more severe ICAS or more arteries with ICAS had higher (P < 0.001) early morning SBP after adjustment for other risk factors. In fully adjusted analysis accounting for SBPs at other time-windows, only early morning SBP (OR, 1.46; 95% CI, 1.14–1.88; P = 0.0029) was associated with ICAS in ≥2 arteries (Table 3).

To further illustrate the association between the presence of ICAS and ambulatory SBP at different time-windows, we computed 3-hourly mean SBPs during the day. Figure 3 shows the OR (95% CI) associated with a 10-mm Hg increase in the 3-hourly mean SBP for the presence of ICAS. After multivariate adjustment, all 3-hourly mean SBPs were significantly associated with the presence of ICAS (OR, 1.28–1.38; P ≤ 0.001; Figure 3A). However, only the mean SBP obtained between 05:00 am and 7:59 am remained significantly associated with ICAS (OR, 1.30; 95% CI, 1.04–1.61; P = 0.019; Figure 3B) when all 3-hourly mean SBPs were forced into a single multivariate model, of which the heuristic shrinkage estimate was 0.89.

### Sensitivity Analysis

By adding an interaction term to the multivariate-adjusted model, further analyses showed a borderline significant interaction between age and early morning SBP (P = 0.09) in relation to ICAS. In patients aged ≥65 years (n = 285) but not in...
patients aged <65 years (n=472, P≥ 0.26), early morning SBP was independently associated with the presence of ICAS (OR, 1.38; 95% CI, 1.02–1.88; P=0.037) and with stenosis at ≥2 intracranial vessels (OR, 1.49; 95% CI, 1.08–2.06; P=0.015).

**Discussion**

Among 757 stroke-free patients with hypertension who underwent both brain CTA and 24-hour ambulatory BP monitoring, a significant and independent association was found between early morning SBP and the presence of ICAS after accounting for established cardiovascular risk factors and SBPs at other time-windows of the day. Patients with ICAS, compared with those without, had significantly higher early morning SBP. Each 10-mm Hg increase in early morning SBP was associated with 26% higher odds for the presence of ICAS and 46% for ICAS in multiple cerebral arteries.

Our findings support previous observations on the association between ambulatory BP at different time-windows and cardiovascular risk. In 519 older patients with hypertension followed up for an average of 41 months, Kario et al showed that morning (2 hours after waking up) SBP was the strongest predictor of stroke compared with SBP at other time covering the clinic, 24-hour period, and separate awake, sleep, evening (2 hours before going to bed), and pre-awake (2 hours before waking up) periods. Each 10-mm Hg increase in morning SBP in older patients with hypertension corresponded to a relative risk of 1.44 for incident stroke. In a random sample of 1700 Danish men and women without major cardiovascular disease followed up for 9.5 years, Hansen et al found that the mean systolic and diastolic BPs at any consecutive 2 hours during the day were significantly predictive of a combined cardiovascular end point, although
the relative risk ratios associated with BPs were not compared between different time-windows.

Our current findings are also consistent with the results of several, though not all, previous studies addressing cardiovascular outcomes and vascular damage associated with morning BP surge. In these studies, morning BP surge was calculated as the average morning BP (2 hours after awakening) minus either the lowest nighttime BP (defined as sleep-trough morning surge) or the average BP during the 2 hours before awakening (preawakening morning surge). In an above-mentioned study, patients with a sleep-trough morning BP surge ≥55 mm Hg (top decile), compared with those in other deciles, had a significantly higher baseline prevalence of multiple cerebral infaracts (57% versus 33%; \( P=0.001 \)) and incidence of stroke (19% versus 7.3%; \( P=0.004 \)). Similarly, in our previous study of an international database, subjects in the top decile of the morning BP surge had a 30% to 50% higher risk for total mortality and fatal and nonfatal combined cardiovascular, cardiac, and coronary events. However, as was seen in the Ohasama study of 1430 subjects, sleep-through morning BP surge predicted cerebral hemorrhage but not ischemic stroke. Recently, Verdecchia et al reported that in 3012 untreated patients with hypertension, a blunted rather than an exaggerated morning BP surge was associated with adverse cardiovascular events. The inconsistent findings on morning BP surge might be attributable to different characteristics of the study populations, such as the extent of morning BP rise and the level of nighttime SBP.

Our study extends previous observations by illustrating a significant association between early morning BP and subclinical cerebral arterial damage. As a common cause of ischemic stroke, ICAS was estimated to account for 33% to 50% of strokes and >50% of transient ischemic attacks in Chinese people. ICAS was the most common vascular lesion in patients with stroke and was highly prevalent in asymptomatic residents aged >50 years or in patients with hypertension as we have observed in our previous and current studies. Experts have, therefore, proposed extending the frontier of stroke prevention to asymptomatic ICAS. Although previous studies demonstrated an independent association between hypertension and ICAS, there were no data on the association between ICAS and ambulatory BPs at different time-windows. Furthermore, the measure of asymptomatic ICAS has been obtained from transcranial Doppler ultrasonography, which has a relatively lower sensitivity in identifying ICAS than brain CTA.

Why SBP in the early morning, compared with SBP at the other time of the day, was independently and most closely associated with cerebrovascular damage remains unexplained. Nonetheless, previous investigations provided some clues. Patients with hypertension with an exaggerated morning BP surge had increased serum C-reactive protein. Plaques biopsied from patients with hypertension with an increased morning BP surge had increased levels of macrophages, T lymphocytes, ubiquitin–proteasome activity, tumor necrosis factor-\( \alpha \), and matrix metalloproteinase-9. Under circumstances of enhanced inflammation and oxidative stress, increased activity of platelet aggregation, and greater activity of the sympathetic and renin–angiotensin–aldosterone systems in the morning, the effect of morning BP on endothelial cells and subsequent atherosclerosis might be greater than at other periods of the day. However, patients with intracranial atherosclerosis may have stiffer arteries and hence more pronounced morning BP surge.

We acknowledge that our study has some limitations. First, we cannot infer any causal relationship from this cross-sectional study. Second, the definitions of consecutive 3-hourly intervals during the day were arbitrary. Our finding on the association between the 3-hourly SBP means and ICAS needs to be validated in future studies with a larger sample size. Third, as the prevalence of ICAS varied substantially between different ethnic populations, our findings may not be directly generalizable to other ethnic populations, especially those with a low prevalence of ICAS. Finally, the information on subject’s sleeping and awake periods was not collected, which makes it impossible to examine whether morning BP surge would be a better indicator than morning BP level for ICAS.

**Perspectives**

In summary, our study has shown for the first time an association between early morning SBP and ICAS. Future analyses are warranted to determine whether these findings translate into prognostic significance toward incident stroke as hard outcome. Randomized controlled trials are necessary to illustrate whether controlling early morning SBP, in addition to diurnal mean SBP, further improves stroke prevention. Although early morning SBP could be measured either by ambulatory or by home BP monitoring, the widespread use of electronic oscillometric BP monitors at home makes it possible to validate whether self-measured home SBP in the morning provides clinical value.

**Acknowledgments**

We gratefully acknowledge the expert assistance of Yijin Liu and Bihua Liu (Shanghai Institute of Hypertension, China) in collecting patient data. We also thank Dr Xueqing Xu, Juan Huang, and Liyun Zhang (Department of Radiology, Ruijin Hospital, Shanghai, China) for their expert assistance in reading brain computerized tomographic angiography images and Professors Ji-Guang Wang (Shanghai Institute of Hypertension, Shanghai, China) and Craig Anderson (The George Institute for Global Health, Sydney, Australia) for editing the article.

**Sources of Funding**

This project is supported, in part, by Project 973 from the Ministry of Science and Technology of China (2009CB521905), Program 863 of National High-Tech Research and Development in China (2012AA02A516), and the Innovation Program of the Shanghai Jiaotong University School of Medicine (BXJ201241).

**Disclosures**

None.

**References**

Novelty and Significance

What Is New?

- Although hypertension is an established risk factor for cerebrovascular disease, only few studies have addressed at what time-window during the day systolic blood pressure was most closely associated with cerebrovascular damage.
- There are limited data on the role of asymptomatic intracranial arterial stenosis in patients with hypertension.

What Is Relevant?

- The occurrence rate of stroke peaks in the morning.
- Intracranial atherosclerotic stenosis is a common cause of ischemic stroke.

Summary

In patients with hypertension, systolic blood pressure in the early morning, compared with other time-windows of the day, was most closely associated with asymptomatic intracranial arterial stenosis.
Association Between Ambulatory Systolic Blood Pressure During the Day and Asymptomatic Intracranial Arterial Stenosis
Chao-Ting Chen, Yan Li, Jin Zhang, Yan Wang, Hua-Wei Ling, Ke-Min Chen, Ping-Jin Gao and Ding-Liang Zhu

Hypertension. 2014;63:61-67; originally published online October 21, 2013;
doi: 10.1161/HYPERTENSIONAHA.113.01838

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://hyper.ahajournals.org/content/63/1/61

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Hypertension can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Hypertension is online at:
http://hyper.ahajournals.org/subscriptions/